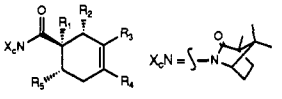
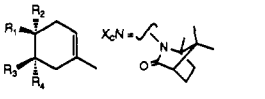
isolated by chromatography and the auxiliary removed in high yield (80–95%) via treatment with $LiOH/H_2O_2$ to afford the acid or LAH to afford the alcohol with excellent recovery of auxiliary (>90%).[3,15]

Remarkably, in view of the modeling results and prior experience, reaction of the crotonate dienophile **4** with isoprene afforded the major cycloadduct **17** (96:4) possessing the unexpected absolute configuration which apparently arises via the s-trans rotamer of **4** as does **14** from **3**.[16,17] Other dienes gave π-facial selectivity (90–92% de) comparable to that seen for the Evans and Oppolzer auxiliaries with the same dienes.[1-3] However, reaction of dienophiles **5** and less surprisingly **6** with isoprene afforded mixtures of adducts **18–19** and **20–21**. Predictably poor π-facial selectivity is observed (~1:1), presumably owing to loss of control over the rotamer population about the C_1–C_2 bond.

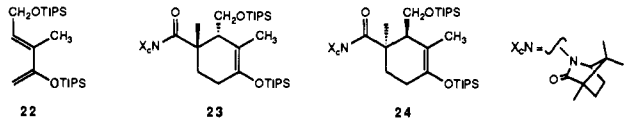


13 $R_1 = CH_3$; $R_2 = R_3 = R_4 = R_5 = H$
14 $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = CH_3$; $R_5 = H$
15 $R_1 = CH_3$; $R_2 = H$; $R_3 = R_4 = CH_3$; $R_5 = H$
16 $R_1 = R_2 = CH_3$; $R_3 = R_4 = R_5 = H$
17 $R_1 = R_2 = R_3 = H$; $R_4 = R_5 = CH_3$



18 $R_1 = CONX_c$; $R_2 = CH_3$; $R_3 = R_4 = H$
19 $R_1 = CH_3$; $R_2 = CONX_c$; $R_3 = R_4 = H$
20 $R_1 = H$; $R_2 = CONX_c$; $R_3 = CH_3$; $R = H$
21 $R_1 = CONX_c$; $R_2 = H$; $R_3 = H$; $R_4 = CH_3$

Somewhat surprisingly, there have been relatively few reported examples of Lewis acid catalyzed cycloadditions of chiral dienophiles with oxygen-substituted dienes, probably as the result of instability of these dienes to the required Lewis acids.[1-4] We have employed triisopropylsilyl (TIPS) protected oxygenated dienes, which has permitted successful cycloadditions with **3–5** in the presence of Et_2AlCl in high yield (89–95%).[13,18] However, as shown in Table I, several TIPS-protected dienes were examined which uniformly exhibited substantially lower π-facial selectivities (1–2:1) than the comparably substituted alkyl dienes. This surprising lack of selectivity may result as a consequence of a very early reactant-like transition state for the cycloaddition reactions involving oxygen-substituted dienes. Thus, the distance-dependent nonbonded interactions normally responsible for the energetic differences which result in π-facial selectivity are much smaller. Significantly, reaction of ent-**3** with the somewhat less reactive and sterically more encumbered diene **22** (2.0 equiv) in the presence of $TiCl_4$ afforded a mixture of the two endo cycloadducts **23** and **24** (88:12) exclusively. The stereochemistry and absolute configuration of **23** was confirmed by X-ray analysis of the derived ketone.[19]



22 **23** **24**

It is interesting to note that the level of diastereoselection in all of these cycloadditions appears to correlate with the diene structure and that the highest π-facial selectivities are observed with dienes bearing substitution at both internal carbons. The generality and possible mechanistic significance of this observation as well as the structure of the reactive dienophile–Lewis acid complexes in solution with respect to the C_1–C_2 rotamer(s) and the development of a more accurate model for the transition-state structure are under investigation. Further studies of cycloaddition reactions of these new chiral dienophiles are also in progress as are studies of the applicability of these auxiliaries to a variety of other reactions amenable to use for asymmetric synthesis.

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Supplementary Material Available: Experimental details for preparation of **1** and **2** and a general procedure for the asymmetric Lewis acid catalyzed Diels–Alder cycloaddition (7 pages). Ordering information is given on any current masthead page.

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(15) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.
(16) The absolute configuration of these adducts was established by correlation with known substances: Sonnet, P. E.; McGovern, T. P.; Cunningham, R. T. *J. Org. Chem.* **1984**, *49*, 4639 and refs 1–3.
(17) This result could also arise by reaction of **4** via other endo and exo transition states both chelated and nonchelated. Since exo/endo selectivity is dependent on the stoichiometry of the Lewis acid, a chelated Lewis acid dienophile complex seems implicated.[2]
(18) Independently, Overman and co-workers have made similar observations: Early, W. G.; Jacobsen, J.; Meier, G. P.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3781. Devine, P. N.; Oh, T. *J. Org. Chem.* **1991**, *56*, 1955.
(19) Details of the single-crystal X-ray analyses of **7** and **23** will appear in a forthcoming full account of these studies.

Asymmetric Synthesis of the Macrolide (+)-A83543A (Lepicidin) Aglycon

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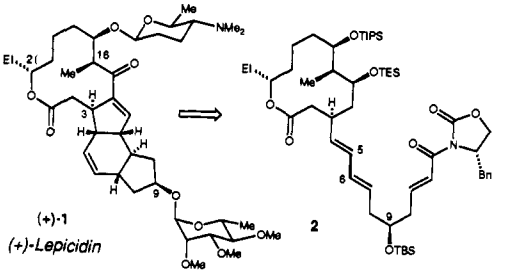
Received December 4, 1991

This communication reports the first synthesis of the structurally unique macrolide A83543A,[1] for which we suggest the name lepicidin. This new natural product has been shown to have potent insecticidal activity, particularly against Lepidoptera larvae.[2] At the time that this project was initiated, the absolute configuration of lepicidin was unknown; consequently, the absolute configuration shown here was presumed on the basis of biogenetic considerations.[3] The synthetic plan for (+)-**1** (Scheme I) was designed around the illustrated intramolecular Diels–Alder[4] reaction of **2**,

Scheme I



which was assembled from a lactonic fragment **3** (Scheme II) and dienic imide **4** (Scheme III) via palladium-catalyzed cross coupling

(1) Kirst, H. A.; Michel, K. H.; Martin, J. W.; Creemer, L. C.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L. D.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Jones, N. D.; Thompson, G. D. *Tetrahedron Lett.* **1991**, *32*, 4839–4842.
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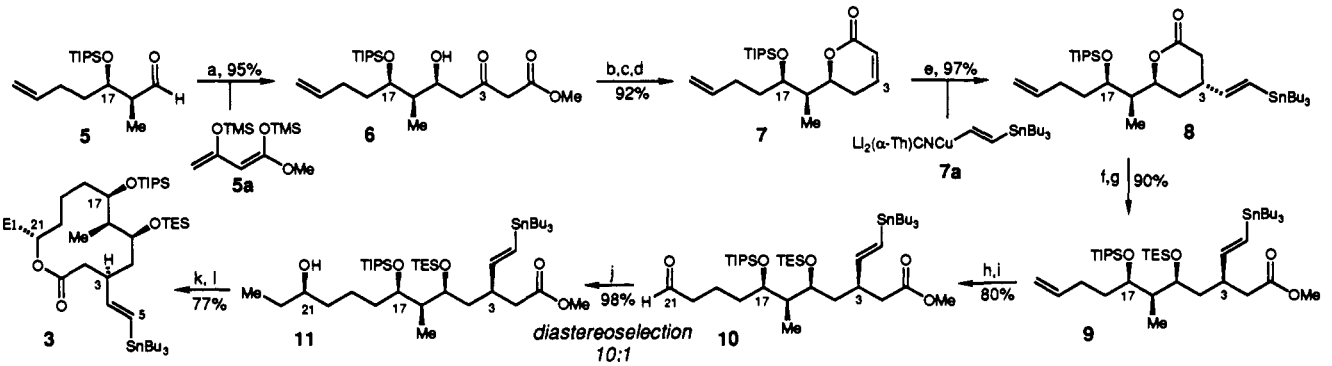
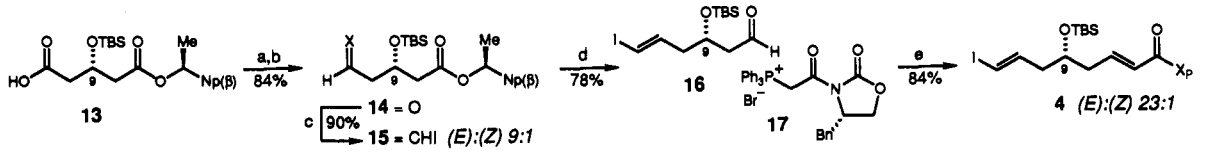
Scheme II[a]



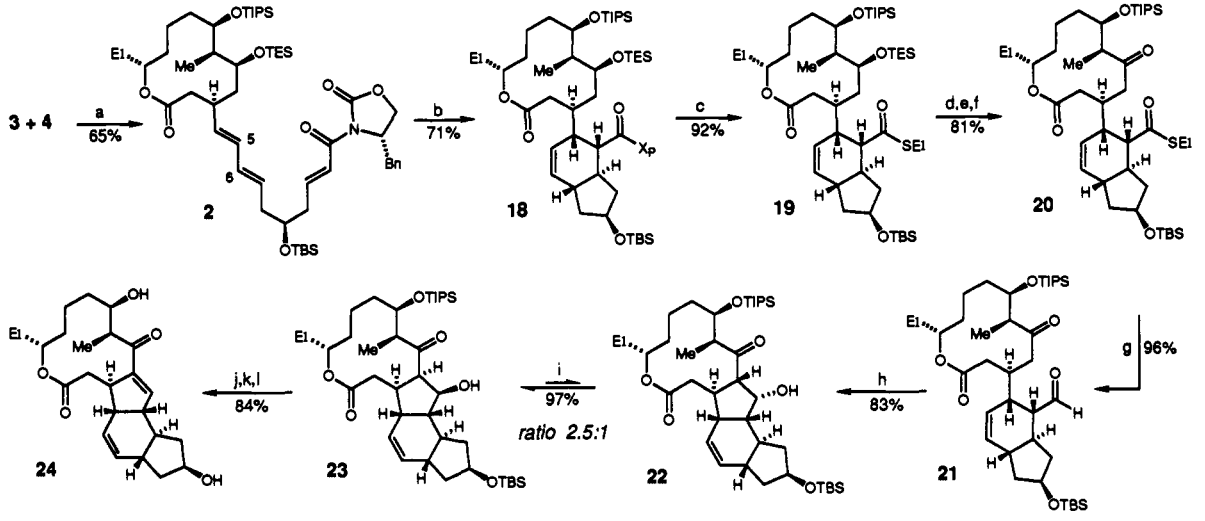
[a] (a) $TiCl_2(OiPr)_2$, CH_2Cl_2, −78 °C. (b) $Me_4NBH(OAc)_3$, AcOH, CH_3CN, −40 °C. (c) PPTS, C_6H_6, 80 °C. (d) MsCl, Et_3N, CH_2Cl_2, room temperature. (e) $BF_3{\cdot}OEt_2$, THF, −78 °C. (f) LiOH, THF, room temperature; CH_2N_2, EtOAc, room temperature. (g) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C. (h) $(Sia)_2BH$, THF, 0 °C; H_2O_2, $NaHCO_3$, THF, 0 °C. (i) $Py{\cdot}SO_3$, DMSO, $(iPr)_2NEt$, CH_2Cl_2, room temperature. (j) Et_2Zn, (+)-*N*,*N*-dibutylnorephedrine, hexane, 0 °C. (k) LiOH, *t*-BuOH, 35 °C. (l) 2,4,6-Trichlorobenzoyl chloride, $(iPr)_2NEt$, THF, room temperature; DMAP, $PhCH_3$, 110 °C.

Scheme III[a]



[a] (a) $BH_3{\cdot}SMe_2$, THF, 0 °C. (b) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −70 °C. (c) CHI_3, $CrCl_2$, dioxane/THF, room temperature. (d) DIBALH, $PhCH_3$, −78 °C. (e) DMAP, $CHCl_3$, room temperature → 60 °C.

Scheme IV[a]



[a] (a) $Pd_2(dba)_3$, $CdCl_2$, $(iPr)_2NEt$, *N*-methylpyrrolidinone, 40 °C. (b) Me_2AlCl, CH_2Cl_2, 0 °C to room temperature. (c) LiSEt, THF, room temperature. (d) AcOH, THF/H_2O, room temperature. (e) TBSCl, ImH, CH_2Cl_2, room temperature. (f) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, room temperature. (g) Et_3SiH, $Pd/CaCO_3/PbO$, acetone, room temperature. (h) NaHMDS, THF, −78 °C. (i) NaHMDS, THF, 0 °C. (j) MsCl, Et_3N, CH_2Cl_2, room temperature. (k) DBU, $PhCH_3$, 60 °C. (l) HF, CH_3CN/THF.

at the C_5–C_6 bond. The successful development of this approach to the synthesis of the lepicidin aglycon is presented in the following discussion.

The synthesis of the macrolide component **3** began with enantiomerically pure aldehyde **5**,[5] which was transformed to β-keto ester **6** (Scheme II) through a highly diastereoselective addition of siloxy diene **5a**[6] (diastereoselection > 20:1). Subsequent reduction,[7] lactonization, and elimination then provided unsaturated δ-lactone **7** in excellent overall yield. The C_3 stereocenter was next installed by the stereoselective conjugate addition of vinylstannane **7a**[8] to lactone **7**. Hydrolysis of lactone **8** followed by immediate esterification and silylation of the intermediate hydroxy

(5) Prepared in 88% yield from 4-pentenal by auxiliary-mediated aldol reaction followed by transamination, protection, and reduction. For an example of this methodology, see: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.

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(7) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

(8) Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Elsworth, E.; Lipshutz, B. H. *Tetrahedron Lett.* **1989**, *30*, 27–30.

acid afforded methyl ester **9**. At this juncture, the terminal olefin in **9** was transformed to aldehyde **10** by regioselective hydroboration and subsequent oxidation.

The isolated C_{21} stereocenter was next established through the (+)-dibutylnorephedrine-catalyzed[9] addition of diethylzinc to aldehyde **10** to provide carbinol **11** as an inseparable 10:1 mixture of diastereomers. Macrolactonization using the method of Yamaguchi[10] afforded macrocycle **3** in 77% yield accompanied by 8% of the readily separable C_{21} epimer. This 16-step reaction sequence provided **3** in 41% overall yield.

The synthesis of diene component **4** began with β-silyloxy acid **13**,[11] which was readily converted to aldehyde **14** (Scheme III). Selective formation of the (*E*)-vinyl iodide was accomplished using Takai's chromium reagent[12] in 6:1 dioxane/THF to provide a 9:1 mixture of olefin isomers, which were separated after the next step. Reduction of ester **15** to aldehyde **16** was followed by the introduction of the oxazolidinone moiety through phosphonium salt **17** to provide the desired *E* unsaturated imide (23:1 ratio). This six-step reaction sequence afforded diene **4** in 42% overall yield.

Fragments **3** and **4** were coupled using a palladium-catalyzed Stille reaction[13] to provide the triene **2** in 65% yield, along with 17% recovered **3**. The subsequent Lewis acid-mediated intramolecular Diels–Alder reaction proceeded with high selectivity to give the desired cycloadduct **18** in 71% yield (Scheme IV).

Removal of the extremely hindered oxazolidinone auxiliary was achieved using Damon's recently reported lithio mercaptide method.[14] Following deprotection and oxidation of **19**, the resulting thioester **20** was efficiently reduced to keto aldehyde **21** by Fukuyama's hydrosilylation procedure[15] using Lindlar's catalyst.

The final ring was then assembled through an intramolecular aldol reaction of **21** to provide a 12:1 mixture of aldol diastereomers **22** and **23**. Unfortunately, the major adduct **22** was inert to dehydration. However, the two diastereomers could be equilibrated via the sodium alkoxide to give a 1:2.5 mixture favoring **23**. Formation and elimination of the mesylate of this adduct provided the differentially protected aglycon. The silyl protecting groups at C_9 and C_{17} could be removed cleanly with HF/acetonitrile to provide the (+)-lepicidin aglycon **24**. The analytical properties of the synthetic material agreed in all respects with those of the natural aglycon[16] with the exception of the optical rotation, which was equal and opposite in sign. This synthesis thus confirms the absolute stereochemical assignment of the natural product previously determined by a combination of X-ray diffraction and degradation.[1]

Acknowledgment. Support has been provided by the National Science Foundation and the National Institutes of Health. An Eli Lilly predoctoral fellowship to W.C.B. is gratefully acknowledged. The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is acknowledged for providing NMR facilities.

Supplementary Material Available: Experimental procedures for all reactions as well as spectral and analytical data for all synthetic intermediates (13 pages). Ordering information is given on any current masthead page.

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(10) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
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(16) We gratefully acknowledge Dr. Herbert Kirst (Eli Lilly and Company) for providing us with an authentic sample of A83543A aglycon for comparison purposes.

Four-Dimensional Heteronuclear Triple Resonance NMR Methods for the Assignment of Backbone Nuclei in Proteins

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Recently, Bax's group demonstrated that three-dimensional (3D) heteronuclear triple resonance NMR spectroscopy of proteins, uniformly enriched with ^{13}C and ^{15}N isotopes, allows sequential resonance assignments in larger proteins (>10 kDa). They proposed an elegant approach which involved recording a set of five or more 3D NMR spectra that correlate chemical shifts of backbone nuclei.[1-3] In order to resolve problems of overlap

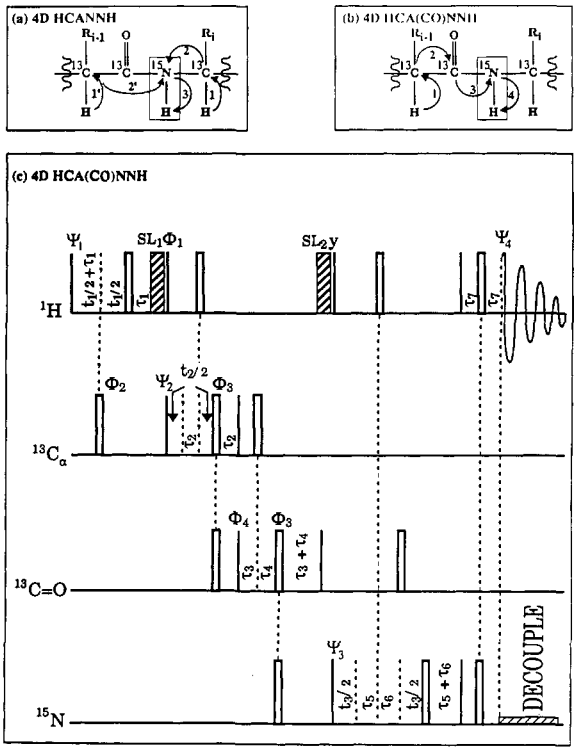

Figure 1. Schematic representation of the magnetization transfer pathways along the polypeptide chain for the HCANNH (a) and the HCA(CO)NNH (b) 4D NMR experiments. In the pulse sequence for the HCA(CO)NNH experiment (c), 90° pulses are depicted as narrow lines while open boxes represent 180° pulses. Cross-hatched boxes represent spin-lock pulses, SL_1 and SL_2, of 1 and 9 ms, respectively.[5,8] Typical values for the delays are as follows: $\tau_1 = 1.5$ ms, $\tau_2 = 1.7$ ms, $\tau_3 = 4.5$ ms, $\tau_4 = 9.5$ ms, $\tau_5 = 2.75$ ms, $\tau_6 = 11.0$ ms, and $\tau_7 = 2.25$ ms. The following phase cycling was employed: $\varphi_1 = 4(y),4(-y)$; $\varphi_2 = x,-x$; $\varphi_3 = 2(x),2(y),2(-x),2(-y)$; $\varphi_4 = 2(x),2(-x)$; $\psi_1 = x$; $\psi_2 = 8(x),8(-x)$; $\psi_3 = x,-x$; $\psi_4 = (x,-x,-x,x),2(-x,x,x,-x),(x,-x,-x,x)$. Unless indicated otherwise, the phase of the remaining pulses is kept at x. Quadrature detection during t_1, t_2, and t_3 was achieved by independently incrementing the phases of ψ_1, ψ_2, and ψ_3 in a States-TPPI manner.[9]

(1) Ikura, M.; Kay, L. E.; Bax, A. *Biochemistry* **1990**, *29*, 4659–4667.
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